ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 50 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see **4.8** and **5.1**). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is $< 0.75 \times 10^9$/l or if the platelet count is $< 50{,}000 \times 10^9$/l. Discontinuation of treatment is recommended if the neutrophil count is $< 0.50 \times 10^9$/l or if the platelet count is $< 25{,}000 \times 10^9$/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Hypersensitivity to any interferon;
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Debilitating medical conditions: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in

patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Other: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets $\geq 100{,}000/mm^3$
- Neutrophil count $\geq 1{,}500/mm^3$
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

PegIntron clinical trial results
The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV (%) of patients					
	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	A vs D B vs D C vs D
Sustained Response 6 Months Post Treatment	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a

single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80
Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.

- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 50 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 50 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 50 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/001
EU/1/00/131/002
EU/1/00/131/003
EU/1/00/131/004
EU/1/00/131/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

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Each vial of PegIntron, powder for solution for injection contains 80 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
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- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;
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4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

PegIntron clinical trial results
The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV (%) of patients					
	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	A vs D B vs D C vs D
Sustained Response 6 Months Post Treatment	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a

single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80
Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.

- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 80 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 80 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 80 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/006
EU/1/00/131/007
EU/1/00/131/008
EU/1/00/131/009
EU/1/00/131/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 100 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see **4.8** and **5.1**). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is $< 0.75 \times 10^9$/l or if the platelet count is $< 50{,}000 \times 10^9$/l. Discontinuation of treatment is recommended if the neutrophil count is $< 0.50 \times 10^9$/l or if the platelet count is $< 25{,}000 \times 10^9$/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Hypersensitivity to any interferon;
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Debilitating medical conditions: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in

patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Other: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets $\geq 100{,}000/mm^3$
- Neutrophil count $\geq 1{,}500/mm^3$
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

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> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

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PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a

single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80
Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.

- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 100 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 100 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 100 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/011
EU/1/00/131/012
EU/1/00/131/013
EU/1/00/131/014
EU/1/00/131/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 120 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see **4.8** and **5.1**). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is $< 0.75 \times 10^9$/l or if the platelet count is $< 50{,}000 \times 10^9$/l. Discontinuation of treatment is recommended if the neutrophil count is $< 0.50 \times 10^9$/l or if the platelet count is $< 25{,}000 \times 10^9$/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Hypersensitivity to any interferon;
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Debilitating medical conditions: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in

patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Other: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets $\geq 100{,}000/mm^3$
- Neutrophil count $\geq 1{,}500/mm^3$
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

PegIntron clinical trial results
The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV (%) of patients					
	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	A vs D B vs D C vs D
Sustained Response 6 Months Post Treatment	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a

single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80
Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.

- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 120 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 120 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 120 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/016
EU/1/00/131/017
EU/1/00/131/018
EU/1/00/131/019
EU/1/00/131/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 150 micrograms of peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol).
Each vial provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated in monotherapy in case of intolerance or contraindication to ribavirin, for the treatment of adult patients with histologically proven chronic hepatitis C who have serum markers for virus C replication, e.g. those who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The optimal treatment for chronic hepatitis C is considered to be the administration of a combination of interferon alfa-2b with ribavirin.
The safety and efficacy of the combination of PegIntron and ribavirin has not yet been documented.

4.2 Posology and method of administration

PegIntron treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

PegIntron monotherapy is administered subcutaneously at a dose of 0.5 or 1.0 microgram/kg once weekly for at least 6 months. The dose should be selected based on the anticipated efficacy and safety (see **4.8** and **5.1**). In patients showing loss of HCV-RNA at 6 months, treatment is continued for an additional 6 months, i.e.1 year of treatment.

If adverse events develop during the course of treatment, it is recommended that the dose of PegIntron be modified to one-half the starting dose once weekly. If persistent or recurrent intolerance develops following dose adjustment, discontinue treatment with PegIntron.

Dose reduction is recommended if the neutrophil count is $< 0.75 \times 10^9$/l or if the platelet count is $< 50{,}000 \times 10^9$/l. Discontinuation of treatment is recommended if the neutrophil count is $< 0.50 \times 10^9$/l or if the platelet count is $< 25{,}000 \times 10^9$/l.

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment (creatinine clearance ≤ 50 ml/minute) (see **5.2**). It is recommended that these patients be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Hypersensitivity to any interferon;
- Autoimmune hepatitis or a history of autoimmune disease;
- Pre-existing severe psychiatric condition or a history of severe psychiatric disorder;
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication;
- Severe renal or hepatic dysfunction;
- Epilepsy and/or compromised central nervous system (CNS) function;
- Pregnancy.

4.4 Special warnings and special precautions for use

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) to interferon alfa-2b have been rarely observed during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Liver function: Discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients. Fluid replacement may be necessary.

Debilitating medical conditions: PegIntron must be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease) or diabetes mellitus prone to ketoacidosis. Caution must be observed also in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. The aetiology has not been defined. These symptoms have been reported more frequently in patients treated with interferon alpha when shosaikoto, a Chinese herbal medicine, is administered concomitantly. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. While this has been reported more often in

patients with chronic hepatitis C treated with interferon alpha, it has also been reported in patients with oncologic diseases treated with interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies has been reported during treatment with alpha interferons. Clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons. Any patient complaining of loss of visual acuity or visual field must have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of PegIntron therapy is recommended in patients with diabetes mellitus or hypertension.

Psychiatric and Central Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects manifested by confusion and other alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alfa-2b have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. In clinical trials using interferon alfa-2b 2.8 % patients overall developed thyroid abnormalities. These were controlled by conventional therapy for thyroid dysfunction. The mechanism by which alpha interferons may alter thyroid status is unknown. Prior to initiation of PegIntron therapy for the treatment of chronic hepatitis C, evaluate serum thyroid-stimulating hormone (TSH) levels. Any thyroid abnormality detected at that time must be treated with conventional therapy. PegIntron treatment may be initiated if TSH levels can be maintained in the normal range by medication. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Other: Due to reports of interferon alfa-2b exacerbating pre-existing psoriatic disease, use of PegIntron in patients with psoriasis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function are recommended in all patients prior to and periodically during treatment with PegIntron. Acceptable baseline values that may be considered as a guideline are:

- Platelets $\geq 100{,}000/mm^3$
- Neutrophil count $\geq 1{,}500/mm^3$
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. PegIntron should not be used during pregnancy (see **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

It is not known whether the components of this medicinal product are excreted in human milk. Therefore, a decision must be made whether to discontinue treatment or discontinue nursing, taking into account the importance of the treatment to the mother.

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Based on a clinical database of 940 PegIntron treated patients of whom 754 received 0.5 to 1.5 microgram/kg for a year, most undesirable effects were mild or moderate in severity and not treatment limiting.

Table 1 Adverse events reported very commonly in clinical trials (≥ 10 % of patients)			
	PegIntron 0.5 microgram/kg once weekly N=315	PegIntron 1.0 microgram/kg once weekly N=297	IntronA 3 MIU three times a week N=303
Application Site Disorders			
Inflammation	44 %	42 %	16 %
Reaction	7 %	10 %	5 %
General Body Discomfort			
Asthenia	12 %	12 %	11 %
Dizziness	8 %	12 %	10 %
Fatigue	43 %	51 %	50 %
Fever	31 %	45 %	30 %
Headache	61 %	64 %	58 %
Flu-like Symptoms	18 %	22 %	19 %
Rigors	34 %	40 %	33 %
Weight Decrease	10 %	11 %	13 %
Gastro-intestinal			
Anorexia	10 %	20 %	17 %
Nausea	21 %	26 %	20 %
Diarrhoea	16 %	18 %	16 %
Abdominal Pain	14 %	15 %	11 %
Musculoskeletal			
Pain	19 %	28 %	22 %
Myalgia	48 %	54 %	53 %
Arthralgia	26 %	25 %	27 %
Psychiatric			
Depression	27 %	29 %	25 %
Anxiety	10 %	9 %	10 %
Concentration Impaired	10 %	10 %	8 %
Insomnia	17 %	23 %	23 %
Irritability	19 %	18 %	24 %
Alopecia	20 %	22 %	22 %
Pharyngitis	12 %	10 %	7 %

Commonly reported undesirable effects (≥ 2 % of patients) were pruritus, skin dry, malaise, sweating increased, right upper quadrant pain, neutropaenia, rash, vomiting, mouth dry, emotional lability, nervousness, dyspnoea, viral infection, somnolence, thyroid disorders, chest pain, dyspepsia, flushing, paresthaesia, coughing, agitation, sinusitis, hypertonia, hyperesthaesia, vision blurred, confusion, flatulence, libido decreased, erythema, eye pain, apathy, hypoesthaesia, loose stool, conjunctivitis, nasal congestion, constipation, vertigo, menorrhagia, menstrual disorder.

Rarely reported events include suicidal ideation and attempted suicide, hearing and retinal disorders, diabetes, hepatopathy and arrhythmia.

Granulocytopaenia (< 0.75 x 10^9/l) occurred in 4 and 7 % and thrombocytopaenia (< 70 x 10^9/l) in 1 and 3 % respectively of patients receiving 0.5 or 1.0 microgram/kg of PegIntron.

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

PegIntron is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol. The average molecular weight of the molecule is approximately 31,300 daltons.

Interferon alfa-2b
Recombinant interferon alfa-2b is obtained from a clone of *E. coli*, which harbours a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes.

In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of Week 4 correlated with the dose of PegIntron.

PegIntron clinical trial results
The safety and efficacy of 48 weeks of treatment with 3 doses of PegIntron (0.5, 1.0, and 1.5 micrograms/kg administered subcutaneously once weekly) vs. IntronA (3 million IU administered subcutaneously 3 times a week) were studied in 1,219 treatment-naive patients with chronic hepatitis C. Table 2 provides sustained virologic response (HCV-RNA below lower limit of detection six months after withdrawal of treatment).

Table 2 Proportion of patients with sustained loss of HCV (%) of patients					
	A	B	C	D	p Value**
Response*	PegIntron 0.5 micro-gram/kg N=315	PegIntron 1.0 micro-gram/kg N=297	PegIntron 1.5 micro-grams/kg N=304	IntronA 3 MIU N=303	A vs D B vs D C vs D
Sustained Response 6 Months Post Treatment	57 (18 %)	73 (25 %)	71 (23 %)	37 (12 %)	0.042 < 0.001 < 0.001
* Serum HCV-RNA is measured by quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml (National Genetics Institute, Culver City, CA) ** Chi-square Test					

Table 3 Sustained Virologic Response by HCV Virus Level (copies/ml) and Genotype				
	Number (%) of Subjects			
	PegIntron 0.5 µg/kg	PegIntron 1.0 µg/kg	PegIntron 1.5 µg/kg	IntronA 3 MIU
Genotype 1				
≤ 2 million	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
> 2 million	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3				
≤ 2 million	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
> 2 million	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)

In general, most side effects were dose-related, and the Quality of Life was less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of IntronA three times a week (see also **4.8**).

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.
Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean PegIntron elimination half life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a

single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see **4.2**).

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to 4 weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80
Solvent for parenteral use: water for injections

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.

- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 150 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 150 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. The reconstituted solution has a concentration of 150 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. Do not use if discolouration is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/021
EU/1/00/131/022
EU/1/00/131/023
EU/1/00/131/024
EU/1/00/131/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/001

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/002

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/003

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/004

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/005

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms - 12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles, 12 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles
and 12 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 50 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/006

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/007

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/008

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/009

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/010

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms - 12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles, 12 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles
and 12 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 80 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/011

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/012

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/013

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/014

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/015

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms - 12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles, 12 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles
and 12 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 100 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/016

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/017

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/018

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/019

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/020

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms - 12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles, 12 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles
and 12 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 120 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 1 vial of powder, 1 ampoule of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/021

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles, 1 cleansing swab

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/022

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 4 vials of powder, 4 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/023

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles, 4 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/024

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 6 vials of powder, 6 ampoules of solvent

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

6 vials of powder, 6 ampoules of solvent
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/025

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms - 12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles, 12 cleansing swabs

Outer packaging (carton)

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles
and 12 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Store at 2°C - 8°C (in a refrigerator)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 150 micrograms

Immediate packaging (label) - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 micrograms/0.5 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron

Immediate packaging (label) - ampoule of solvent

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Solvent for PegIntron
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.7 ml